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## **Ischemic Burden by 3-Dimensional Myocardial Perfusion Cardiovascular Magnetic Resonance: Comparison With Myocardial Perfusion Scintigraphy**

Jogiya, R ; Morton, G ; De Silva, K ; Reyes, E ; Hachamovitch, R ; Kozerke, S ; Nagel, E ; Underwood, S R ; Plein, S

**Abstract:** Background: The extent and severity of ischemia on myocardial perfusion scintigraphy (MPS) is commonly used to risk-stratify patients with coronary artery disease. Estimation of ischemic burden by cardiovascular magnetic resonance (CMR) with conventional 2-dimensional myocardial perfusion methods is limited by incomplete cardiac coverage. More recently developed 3-dimensional (3D) myocardial perfusion CMR, however, provides whole-heart coverage. The aim of this study was to compare ischemic burden on 3D myocardial perfusion CMR with 99mTc-tetrofosmin MPS. Methods and Results—Forty-five patients who had undergone clinically indicated MPS underwent rest and adenosine stress 3D myocardial perfusion and late gadolinium enhancement CMR. Summed stress and rest scores were calculated for MPS and CMR using a 17-segment model and expressed as a percentage of the maximal possible score. Ischemic burden was defined as the difference between stress and rest scores. 3D myocardial perfusion CMR and MPS agreed in 38 of the 45 patients for the detection of any inducible ischemia. The mean ischemic burden for MPS and CMR was similar ( $7.5 \pm 8.9\%$  versus  $6.8 \pm 9.5\%$ , respectively,  $P=0.82$ ) with a strong correlation between techniques ( $rs=0.70$ ,  $P<0.001$ ). In a subset of 33 patients who underwent clinically indicated invasive coronary angiography, sensitivities and specificities of the 2 techniques to detect angiographic coronary artery disease were similar (McNemar  $P=0.45$ ). Conclusions—3D myocardial perfusion CMR is an alternative to MPS for detecting the presence and rating the severity of ischemia.

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## Ischemic Burden by 3-Dimensional Myocardial Perfusion Cardiovascular Magnetic Resonance Comparison With Myocardial Perfusion Scintigraphy

Roy Jogiya, MBBS; Geraint Morton, MBBS, PhD; Kalpa De Silva, MBBS, PhD;  
Eliana Reyes, MD; Rory Hachamovitch, MD; Sebastian Kozerke, PhD; Eike Nagel, MD, PhD;  
S. Richard Underwood, MD\*; Sven Plein, MD, PhD\*

**Background**—The extent and severity of ischemia on myocardial perfusion scintigraphy (MPS) is commonly used to risk-stratify patients with coronary artery disease. Estimation of ischemic burden by cardiovascular magnetic resonance (CMR) with conventional 2-dimensional myocardial perfusion methods is limited by incomplete cardiac coverage. More recently developed 3-dimensional (3D) myocardial perfusion CMR, however, provides whole-heart coverage. The aim of this study was to compare ischemic burden on 3D myocardial perfusion CMR with  $^{99m}\text{Tc}$ -tetrofosmin MPS.

**Methods and Results**—Forty-five patients who had undergone clinically indicated MPS underwent rest and adenosine stress 3D myocardial perfusion and late gadolinium enhancement CMR. Summed stress and rest scores were calculated for MPS and CMR using a 17-segment model and expressed as a percentage of the maximal possible score. Ischemic burden was defined as the difference between stress and rest scores. 3D myocardial perfusion CMR and MPS agreed in 38 of the 45 patients for the detection of any inducible ischemia. The mean ischemic burden for MPS and CMR was similar ( $7.5 \pm 8.9\%$  versus  $6.8 \pm 9.5\%$ , respectively,  $P=0.82$ ) with a strong correlation between techniques ( $rs=0.70$ ,  $P<0.001$ ). In a subset of 33 patients who underwent clinically indicated invasive coronary angiography, sensitivities and specificities of the 2 techniques to detect angiographic coronary artery disease were similar (McNemar  $P=0.45$ ).

**Conclusions**—3D myocardial perfusion CMR is an alternative to MPS for detecting the presence and rating the severity of ischemia. (*Circ Cardiovasc Imaging*. 2014;7:647-654.)

**Key Words:** coronary artery disease ■ cardiac-gated single-Photon emission computer-assisted tomography  
■ magnetic resonance imaging ■ myocardial infarction ■ myocardial ischemia

Myocardial perfusion cardiovascular magnetic resonance (CMR) has become an established method for the non-invasive diagnosis of coronary artery disease (CAD).<sup>1,2</sup> It is accurate and in recent studies was shown to be noninferior to single-photon emission computer-assisted tomography myocardial perfusion scintigraphy (SPECT MPS).<sup>1,3</sup> However, the cardiac coverage provided by conventional myocardial perfusion CMR methods is limited to 3 short-axis sections that cover 16 of the 17 myocardial segments defined by guidelines but with variable gaps between the acquired sections.<sup>4</sup> Although this may be sufficient for diagnostic purposes, the selective spatial coverage may prevent an accurate measurement of ischemic burden.<sup>5</sup> In clinical practice, ischemic burden is most commonly measured by MPS. It is an important prognostic factor

in CAD<sup>6,7</sup> and in accordance with guidelines can help identify patients who will benefit most from revascularization compared with medical therapy.<sup>8,9</sup>

### Clinical Perspective on p 654

In a recent subanalysis of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) study, ischemic burden was compared between MPS and conventional 2-dimensional CMR perfusion. Although there was good agreement for overall ischemic burden, discrepancies in the detection of ischemia versus scar were noted, thought to be related at least in part to the differences in cardiac coverage of perfusion CMR and perfusion MPS and also between perfusion MPS and late gadolinium enhancement (LGE) CMR.<sup>10</sup>

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From the King's College London BHF Centre of Excellence, NIHR Biomedical Research Centre and Wellcome Trust and EPSRC Medical Engineering Centre at Guy's and St. Thomas' NHS Foundation Trust, Division of Imaging Sciences, The Rayne Institute, London, United Kingdom (R.J., G.M., S.K., E.N., S.P.); King's College London BHF Centre of Excellence, NIHR Biomedical Research Centre at Guy's and St. Thomas' NHS Foundation Trust, Cardiovascular Division, The Rayne Institute, London, United Kingdom (K.D.S.); Biomedical Research Unit, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, United Kingdom (E.R., S.R.U.); Section of Cardiovascular Imaging, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH (R.H.); Institute for Biomedical Engineering, University and ETH Zurich, Switzerland (S.K.); and Multidisciplinary Cardiovascular Research Centre & Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, United Kingdom (S.P.).

\*Drs Underwood and Plein contributed equally to this work.

Correspondence to Sven Plein, MD, PhD, Multidisciplinary Cardiovascular Research Centre & Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, LS2 9JT, United Kingdom. E-mail s.plein@leeds.ac.uk

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Recently proposed 3-dimensional (3D) myocardial perfusion CMR techniques overcome the problem of limited cardiac coverage and are also accurate in the detection of CAD.<sup>5,11–13</sup> Measurements of ischemic burden from 3D myocardial perfusion CMR have been shown to agree with invasive indices of myocardium at risk<sup>12</sup> and to reduce following percutaneous coronary intervention.<sup>14</sup> However, a direct comparison with MPS has not previously been reported.

The main objective of this study was, therefore, to compare ischemic burden between MPS and 3D myocardial perfusion CMR. Diagnostic accuracy of the 2 methods against invasive coronary angiography was also assessed in a subset of patients.

## Methods

### Patient Population

The study was approved by the local research ethics committee, and all subjects gave written informed consent to participate. Forty-six patients routinely referred for MPS to the Royal Brompton Hospital, London, United Kingdom, were consecutively recruited to undergo CMR within the following 14 days. The MPS studies were reported as part of clinical routine and the report available to the referring physician to guide patient management. Exclusion criteria were contraindications to CMR or adenosine stress and the presence of atrial fibrillation. On the procedure day, a full medical history and examination were undertaken. Symptoms of chest pain were recorded in accordance with the Canadian Cardiovascular Society angina grading scale. A resting ECG was analyzed for the presence of Q waves or bundle branch block using defined Minnesota criteria.<sup>15</sup>

### MPS Acquisition

All patients underwent 1-day stress–rest<sup>16</sup> ECG-gated <sup>99m</sup>Tc-tetrofosmin MPS using a dual-headed gamma camera (Philips CardioMD) fitted with <sup>153</sup>Gd transmission sources. Patients were asked to abstain from caffeine for 12 hours before the study and to have only a light breakfast. Adenosine was infused at 140 µg/kg/min for 6 minutes combined with semisupine exercise on a bicycle ergometer in 2-minute stages of 25 W, 50 W, and 75 W if tolerated. In patients with left bundle branch block or bifascicular block, adenosine was infused without exercise. A 250 MBq <sup>99m</sup>Tc-tetrofosmin was injected 2 minutes before the end of stress with imaging 45 to 60 minutes after injection. Three hours later, 750 MBq <sup>99m</sup>Tc-tetrofosmin was given at rest 5 minutes after 200 µg sublingual glyceryl trinitrate, with imaging 45 to 60 minutes later. The total effective radiation dose was 8 mSv.

### MPS Interpretation

For the purpose of this study, all MPS studies were reported by an observer blinded to all clinical data and the previous clinical MPS report. The analysis undertaken for the purpose of this study was not made available to the patient's clinician. Transverse tomograms of the left ventricle were reconstructed using iterative reconstruction on a Hermes workstation (Hermes Medical Systems, Stockholm). Transaxial slices were reoriented to obtain short-axis, horizontal long-axis, and vertical long-axis views of the left ventricle. Attenuation correction and resolution recovery were used. Unprocessed planar images were displayed in the cine format to assess quality and to assess patient motion and attenuation. Image artifact was scored on a 4-point scale from 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Image quality was scored on a similar scale using the reconstructed tomograms taking into account the severity of artifact score and overall clinical value as follows:

1. Q3: excellent quality images with no artifact
2. Q2: good quality images with total artifact score of ≤2
3. Q1: adequate quality images with total artifact score of ≥3
4. Q0: inadequate quality images with artifact severe enough to affect diagnostic quality

The tomographic slices were divided into 17 segments<sup>4</sup> and mean segmental counts were graded semiquantitatively by an experienced observer: 0=normal uptake (≥70% of maximum activity), 1=mild reduction (50%–69%), 2=moderate reduction (30%–49%), 3=severe reduction (10%–29%), and 4=absent uptake (0%–9%). The summed stress score and summed rest score were obtained by adding segmental scores, and the summed difference score (ie, summed stress score–summed rest score) expressed as a percentage of 68, the theoretical maximum score, was used as a measure of total ischemic burden.<sup>17</sup>

Each study was also classified as normal or showing reversible, fixed, or mixed defects. A subjective confidence score of 3 (definite confidence), 2 (moderate confidence), 1 (mild confidence), to 0 (uncertain) was assigned to the classification.

### CMR Acquisition

All subjects were scanned in a supine position using a 3T magnetic resonance scanner (Achieva; Philips Healthcare, Best, the Netherlands) equipped with dual-source parallel radio frequency transmission (multitransmit) technology<sup>18</sup> and a 6-channel cardiac phased array receiver coil. Patients were asked to refrain from caffeine-containing substances for 12 hours before CMR. Subjects were monitored throughout the scan with a 4-lead vectorcardiogram, respiratory belt, and blood pressure monitoring. For perfusion imaging, a 3D spoiled turbo gradient echo sequence was used (repetition time/echo time/flip angle 1.8 ms/0.7 ms/15°, saturation prepulse delay 150 milliseconds, acquisition timed to end systole, 75% partial Fourier sampling in the ky and kz direction and an elliptical *k*-space shutter, 10-fold *k*-*t* acquisition with 49 training profiles leading to a net acceleration of 7.0, total number of acquired profiles 106, which results in an acquisition time per heartbeat of 191 milliseconds [106×1.8 milliseconds], *k*-*t* principal component analysis reconstruction,<sup>11,19</sup> reconstruction of 12 contiguous slices of 5 mm thickness, field of view 350×245 mm<sup>2</sup>, acquired voxel size 2.3×2.3×5 mm<sup>3</sup>, interpolated to 1.5×1.5×5 mm<sup>3</sup>).

Stress perfusion images were acquired during intravenous adenosine-induced hyperemia administered at 140 µg/kg/min. An intravenous bolus of 0.075 mmol/kg gadobutrol (Gadovist, Bayer, Germany) was administered at a rate of 4.0 mL/s followed by a 20-mL saline flush (Spectris Solaris power injector, PA).

Stress perfusion CMR was followed by cine imaging covering the left ventricle in 10 to 12 short-axis sections and a rest perfusion scan performed 15 minutes later using the same concentration and volume of contrast agent as for stress perfusion. LGE images (0.15 mmol/kg cumulative dose) were acquired in the same short-axis geometry after a further 15 minutes using a conventional method.<sup>20</sup>

### CMR Analysis

An experienced observer blinded to all previous test results analyzed the CMR images using standard software (ViewForum, Philips Healthcare, Best, the Netherlands). The CMR data and analysis were not made available to the patient's clinician. Stress and rest perfusion scans were viewed simultaneously. Image artifacts were scored using a 4-point scale from 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The artifact was categorized as breathing related, subendocardial rim artifact, or related to the reconstruction of undersampled data. Image quality was graded in the same way as MPS on a score of Q3 to Q0.

An inducible perfusion defect was considered to be present if there was reduced or delayed segmental delivery of contrast to the myocardium during stress persisting for >4 cardiac cycles, not present on the rest perfusion images. This analysis strategy is consistent with recommended reporting guidance to exclude artifacts.<sup>21</sup> For calculation of ischemic burden, each segment was scored on a 5-point scale taking into account the transmural extent of the stress perfusion defect: 0 normal (0%–24%), 1 mild defect (25%–49%), 2 moderate defect (50%–74%), 3 severe reduction (75%–100%), and 4 thinned with persistent absent contrast delivery. Viable myocardium was assessed using the LGE images, scored in a similar way for transmural extent of enhancement with 0 representing no enhancement, 1 mild enhancement (1%–24%),



2 moderate enhancement (25%–49%), 3 severe enhancement (50%–74%), and 4 transmural enhancement ( $\geq 75\%$ ).

As for MPS, a confidence score of 3 (definite confidence), 2 (moderate confidence), 1 (mild confidence), to 0 (uncertain) was subjectively assigned to the classification.

In accordance with MPS analysis, the summed stress score and summed rest score taken from the LGE images were obtained by adding segmental scores, and the summed difference score (ie, summed stress score–summed rest score) was expressed as a percentage of 68, the theoretical maximum score, was used as a measure of total ischemic burden.

### Whole-Heart Versus 3-Slice Comparison

We aimed to determine whether ischemic burden measured from whole-heart myocardial perfusion CMR agrees more closely with SPECT than the conventional 2D myocardial perfusion CMR methods, which usually provide only 3-slice coverage. Although no original 2D CMR data were acquired in this study, analysis of 3 slices of the whole-heart data sets was considered a reasonable approximation for conventional 2D 3 slice methods. Several limitations of this approach relating to cardiac phase, spatial, and temporal resolution are explicitly acknowledged and will be discussed. For this analysis, all data sets were reanalyzed after 4 weeks by a reviewer blinded to all previous analyses and clinical data. Only slices 3, 7, and 11, representing apical, midmyocardial, and basal sections, were shown to the reviewer. All scoring was repeated using a 16-segment model that excluded the true apex.

### Reproducibility

Analysis of MPS and CMR was repeated by the same reader at a remote time in a subset of 16 patients.

### Coronary Angiography

Treating physicians decided the clinical management of patients including the referral for invasive angiography based on the clinical MPS report and all other clinical information. Data obtained as part of this research were not released to treating physicians. Clinically indicated coronary angiography performed within 8 weeks of MPS was reviewed for this study. X-ray angiograms were reported by an experienced cardiologist blinded to the other studies. Significant CAD was defined as  $\geq 70\%$  stenosis of a first-order coronary artery measuring  $\geq 2$  mm in diameter or LMS stenosis  $\geq 50\%$ , by quantitative coronary angiography (Medcon Ltd, Tel Aviv, Israel).

### Statistical Analysis

Data were analyzed using IBM SPSS v19 (SPSS, Chicago, IL). Differences in mean ischemic burden used Bland–Altman analysis and Wilcoxon test. Comparisons of ischemic burden used Spearman correlation. The comparison of ischemia burden of CMR perfusion with MPS in 45 patients will deliver a power of  $\geq 80\%$  at a 95% significance level to determine agreement between the tests. The intraobserver variability of perfusion analysis was calculated using the  $\kappa$  coefficient. McNemar test was used to compare the accuracy of the noninvasive test against the standard of coronary angiography. For all analyses  $P < 0.05$  was considered significant.

## Results

### Patients

Of the 46 patients recruited, one was excluded because of a technical fault during the CMR study, in which contrast was injected too early preventing acquisition of the first pass perfusion under hyperemia. Forty-five patients (31 men, mean age 59) thus formed the population for analysis. The indication for referral was diagnosis of CAD in 26 patients (58%) without a prior history of CAD. In this population, the pretest likelihood

of underlying CAD was 37.8% (95% CI, 31.8%–43.9%). Nineteen patients had a previous history of CAD with 15 having had previous documented myocardial infarction (Table 1). Thirty-nine patients experienced symptoms during CMR stress perfusion compared with 35 patients during MPS ( $P = 0.27$ ).

### Myocardial Perfusion Scintigraphy

Hemodynamic data are shown in Table 2. All studies were considered interpretable with a median image quality score of 3 and a median confidence score of 2. The main artifacts reported were motion (6/45) and attenuation (6/45). Intraobserver variability showed agreement in 15 of 16 cases ( $\kappa = 0.88$ ) for the detection of ischemia.

### CMR Imaging

The mean time from MPS to CMR was 9 days (range, 3–14 days). Mean scan time was 47 minutes (SD=4). Hemodynamic

**Table 1. Patient Demographics**

| Parameter  | Data (%)       |
|--|----------------|
| Number   | 45             |
| Male   | 32 (71.1)      |
| Age, y   | 58.9 $\pm$ 7.7 |
| Range  | 44–76          |
| BMI, kg/m <sup>2</sup>                                       | 25.8 $\pm$ 2.8 |
| Previous myocardial infarction                               | 15 (33.3)      |
| Previous coronary intervention                               | 16 (35.6)      |
| Normal LV function (EF>60%)                                  | 41 (91.1)      |
| Canadian Cardiovascular Society Angina Grading Scale         |                |
| No pain or atypical symptoms                                 | 27 (60.0)      |
| Class 1  | 9 (20.0)       |
| Class 2  | 6 (13.3)       |
| Class 3  | 3 (6.7)        |
| Class 4  | 0 (0)          |
| Baseline ECG   |                |
| Q wave   | 7 (15.6)       |
| Left bundle branch block                                     | 5 (11.1)       |
| Right bundle branch block                                    | 1 (2.2)        |
| Cardiovascular risk factors                                  |                |
| Diabetes mellitus  | 16 (35.6)      |
| Dyslipidemia   | 41 (91.1)      |
| Current smoker   | 12 (26.7)      |
| Hypertension   | 38 (84.4)      |
| Family history   | 22 (48.9)      |
| Medications  |                |
| Aspirin  | 41 (91.1)      |
| Clopidogrel  | 7 (15.6)       |
| $\beta$ -blocker   | 27 (60.0)      |
| Calcium channel blocker                                      | 5 (11.1)       |
| Statin   | 41 (91.1)      |
| Angiotensin enzyme inhibitor or angiotensin receptor blocker | 33 (73.3)      |
| Nitrate  | 12 (17.8)      |

BMI indicates body mass index; EF, ejection fraction; and LV, left ventricle.

**Table 2. Hemodynamic Data**

|     | Rest       |            |          | Stress     |            |          |
|-----|------------|------------|----------|------------|------------|----------|
|     | MPS        | CMR        | <i>P</i> | MPS        | CMR        | <i>P</i> |
| HR  | 72.9±11.6  | 72.0±11.6  | 0.42     | 102.2±17.7 | 89.5±13.6  | <0.0001  |
| SBP | 139.8±18.7 | 135.2±12.6 | 0.08     | 153.3±23.3 | 130.5±22.6 | 0.008    |
| DBP | 81.6±13.4  | 80.0±19.6  | 0.4      | 88.1±21.2  | 80.1±12.7  | <0.0001  |
| RPP | 10250±2408 | 9825±2769  | 0.19     | 15810±4365 | 11841±3568 | <0.0001  |

CMR indicates cardiovascular magnetic resonance; DBP, diastolic blood pressure; HR, heart rate; MPS, myocardial perfusion scintigraphy; RPP, rate pressure product; and SBP, systolic blood pressure.

data are shown in Table 2. Compared with MPS, there were significant differences in stress blood pressure and heart rate, reflecting the differing stress regimes. All 45 CMR studies were of interpretable quality. The median image quality score was 3 and the median confidence score was 3. The main artifacts seen were subendocardial dark rim artifacts in 7 patients (16%) and breathing artifact in 4 patients (9%). There was 100% intraobserver agreement for the presence of ischemia ( $\kappa=1$ ).

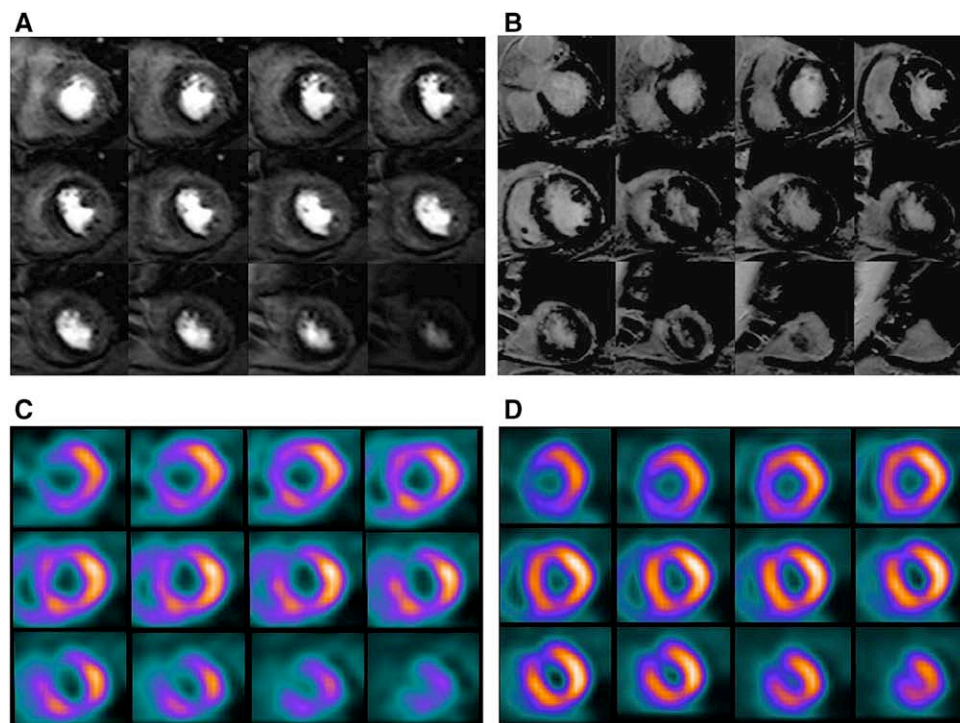
### Comparison of Ischemic Burden by MPS and CMR

MPS and CMR agreed for the presence or absence of inducible ischemia in 38 of 45 patients (84%; Figures 1 and 2). The mean ischemic burden by MPS in all 45 patients was 7.5% (SD, 8.9; range, 0–29.4) and by CMR 6.8% (SD, 9.5; range, 0–33.8)

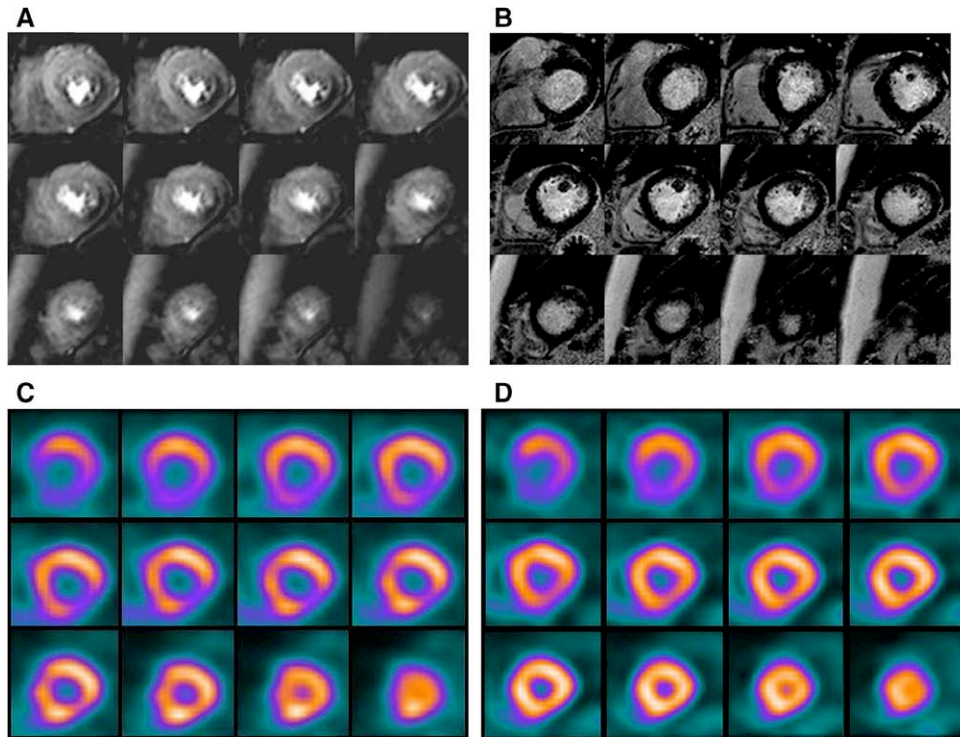
with good correlation and no significant differences between methods ( $r=0.70$ ;  $P=0.82$ ). In the 38 patients in whom the tests agreed, the correlation for ischemic burden was stronger ( $r=0.96$ ;  $P<0.0001$ ; Figure 3). The mean bias for ischemic burden between the 2 methods (CMR minus MPS) was  $-0.62\%$  (95% limit of agreement,  $-14.3$  to  $13.1\%$ ; Figure 4).

Twelve patients had an ischemic burden  $>10\%$  on MPS, and of these, CMR ischemic burden was  $>10\%$  in 11 patients. Conversely, 2 patients had CMR ischemic burden  $>10\%$  but  $<10\%$  by MPS, although the differences were small (10.3% and 10.3% by CMR versus 8.8% and 7.5% by MPS).

When only 3 short-axis slices were used for CMR analysis, the mean ischemic burden was lower at 5.7% (SD, 8.2). There was no significant difference in the ischemic burden between



**Figure 1.** Images from a 47-year-old man with atypical chest pain and multiple risk factors for coronary artery disease are shown. The patient had no known prior myocardial infarction. **A** and **B**, Cardiovascular magnetic resonance (CMR) perfusion scans during adenosine stress and late gadolinium enhancement (LGE) CMR. A perfusion defect is seen in the anterior and anteroseptal segments from the base to the apex extending into the inferior wall. LGE shows subendocardial scar in the septal segments from the mid ventricle to the apex. The ischemic burden by CMR was 20.5%. **C** and **D**, Rest and stress myocardial perfusion scintigraphy (MPS). Stress MPS shows extensive and profound inducible ischemia involving most of the left anterior descending (LAD) coronary artery territory and further inferior changes corresponding with the stress CMR images. Rest MPS shows reduced uptake in the LAD territory toward and including the apex that is less marked than on the stress images. The study was reported as showing partial infarction in the LAD territory with a large area of peri-infarct ischemia. The ischemic burden by MPS was 19.8%. Invasive X-ray angiography showed an occlusion of the proximal left anterior descending coronary artery with collateral supply from the right coronary artery, which had a mid course stenosis.



**Figure 2.** Images from a 58-year-old man with a previous myocardial infarction and subsequent revascularization with ongoing chest pain are shown. **A** and **B**, Cardiovascular magnetic resonance (CMR) perfusion scan during adenosine stress and corresponding late gadolinium enhancement images. A subendocardial perfusion defect is seen in the basal inferolateral wall extending to the mid inferolateral wall. Late gadolinium enhancement CMR shows a small area of subendocardial scar in the same region, but the perfusion deficit extends beyond the equivalent imaging plane. The ischemic burden by CMR was 8.8%. **C** and **D**, Stress and rest myocardial perfusion scintigraphy (MPS) imaging shows corresponding limited partial-thickness scarring in the basal inferolateral region with mild superimposed and peri-infarct ischemia extending up to the mid inferolateral region. The ischemic burden by MPS was 7.4%. The coronary angiogram showed a significant stenosis in a large first obtuse marginal branch.

MPS and 3-slice perfusion ( $P=0.12$ ). However, there was a significant difference in ischemic burden between whole-heart CMR and 3-slice CMR perfusion analysis ( $P=0.03$ ). There was good correlation between 3-slice analysis and MPS ischemic burden ( $rs=0.72$ ) and excellent correlation with whole-heart CMR analysis ( $rs=0.97$ ).

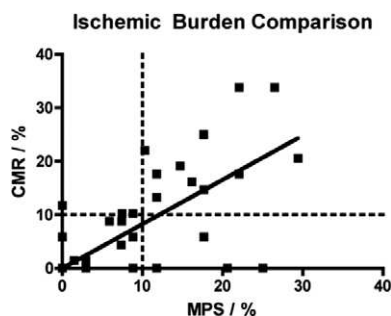
### Scar Burden

CMR and MPS agreed for the presence or absence of myocardial scar in 38 of 45 patients (84%). Scar was detected by LGE CMR in 14 of 45 patients (31%) and in 11 of these also by MPS. Four patients had scar reported on MPS that was

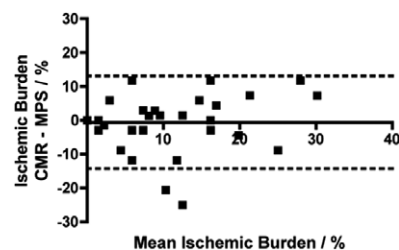
not present on LGE CMR. Taking CMR as the reference, the sensitivity of MPS for scar was 79% (95% CI, 49%–94%) and specificity 87% (95% CI, 69%–96%). The mean scar burden was higher with MPS than CMR (4.9% SD 10% versus 3% SD 6.8%), but this was not statistically significant ( $P=0.06$ ). In all 45 patients, the correlation between the 2 tests for scar burden was good ( $rs=0.73$ ), and in the 38 cases in which CMR and SPECT agreed, there was stronger agreement ( $rs=0.99$ ).

### Diagnostic Accuracy Against Coronary Angiography

Of the 45 patients, 33 underwent coronary angiography for clinical reasons, of whom 17 were found to have significant



**Figure 3.** Correlation between myocardial perfusion scintigraphy (MPS) and cardiovascular magnetic resonance (CMR) for ischemic burden in the patients where there was agreement between the techniques (38/45): The dotted line indicates 10% ischemic burden.



**Figure 4.** Bland–Altman analysis of ischemic burden between the techniques in the cohort of patients where there was agreement between the techniques (38/45). Bland–Altman analysis showed a mean bias for ischemic burden between the 2 methods of 0.62% (95% CI, –7.98% to 9.21%). CMR indicates cardiovascular magnetic resonance; and MPS, myocardial perfusion scintigraphy.



coronary disease (disease prevalence 52%). The overall sensitivity, specificity, and diagnostic accuracy of MPS were 94% (95% CI, 71%–100%), 63% (95% CI, 39%–87%), and 79%. The positive and negative predictive values were 72.7% and 90.9%, respectively. The sensitivity, specificity, and diagnostic accuracy of CMR was 94% (95% CI, 71%–100%), 81% (95% CI, 54%–95%), and 88% (Table 3). The positive and negative predictive values were 84.2% and 92.9%, respectively. Diagnostic performance of both tests depended on image quality and confidence scores (Table 4). The overall accuracy of the 2 techniques did not differ significantly (McNemar  $P=0.45$ ).

## Discussion

3D myocardial perfusion CMR has become feasible because of increased speed of data acquisition.<sup>11</sup> Its value for the calculation of ischemic burden was first suggested in a phantom study, which showed that 3D imaging was more reliable than the conventional 2D techniques.<sup>5</sup> Subsequent studies demonstrated the feasibility of measuring ischemic burden, a reduction in ischemic burden after coronary intervention<sup>14</sup> and a strong correlation with the invasively derived Duke jeopardy score.<sup>12</sup> The current study has now shown that ischemic burden by 3D myocardial perfusion CMR agrees closely with the clinical reference standard of MPS and that both methods have similar accuracy for the detection of angiographically significant CAD.

The presence of myocardial ischemia is relevant prognostically, and an ischemic burden >10% of total myocardium is a threshold above which revascularization leads to better outcomes than with medical therapy alone.<sup>17,22</sup> Most data on ischemic burden have been derived from MPS,<sup>6,7,17,22</sup> justifying the comparison of 3D myocardial perfusion CMR with MPS in this study. In addition to the close overall agreement between the techniques we found that in 11 of 12 patients with an ischemic burden >10% by MPS, the ischemic burden by CMR was also >10%. Conversely, CMR only slightly overestimated ischemic burden in 2 patients with an ischemic burden <10% by MPS.

This suggests that the 10% MPS threshold for improved outcome with intervention might also be used for 3D myocardial perfusion CMR, but prospective studies will be required to confirm this.

## Scar Burden

LGE CMR is an established technique for the detection of myocardial scarring, and it is sensitive to even small amounts

of infarction.<sup>20,23</sup> MPS is widely used for the detection infarction and it is well validated for its quantification although it is less sensitive than CMR for small areas of infarction because of its lower spatial resolution.<sup>24</sup> In this study, there was overall good correlation between CMR and MPS for the detection and quantification of scar, but numbers were too small to formally assess the relationship between infarct size and agreement between the two methods.

## Detection of CAD

In the subgroup of patients that underwent coronary angiography, the sensitivity of 3D perfusion CMR was similar to previous studies. MPS had a similar high sensitivity but the specificity was nonsignificantly lower because of 6 false-positive cases. A breakdown into image quality and confidence scores showed that diagnostic performance was greater with better quality images for both tests.

## Whole-Heart Versus 3-Slice Analysis

Because of its full cardiac coverage, estimates of ischemic burden from 3D myocardial perfusion CMR may correlate better with SPECT measurements than estimates based on 2D myocardial perfusion CMR. To investigate this question, we calculated ischemic burden from 3 slices of the whole-heart data set and compared it with whole-heart CMR analysis using all slices of the 3D data set and SPECT data. We acknowledge that this approach cannot be considered a full substitute for original 2D acquisition. For example, as compared to a previously published 2D acquisition method using  $k$ - $t$  acceleration,<sup>25</sup> the selected 3 slices of the 3D stack have lower in-plane spatial resolution (2.3 mm versus 1.4 mm), a longer temporal acquisition window (193 milliseconds versus 120 milliseconds), but have thinner slices (5 mm versus 10 mm), require faster acceleration (10× versus 5×), and acquire all of the data in an end-systolic heart phase instead of at 3 different cardiac phases. These differences between 2D acquisition and the simulation we used in our study may affect the detection of subendocardial ischemia in slices acquired during diastolic time points or during rapid motion. Our analysis can, therefore, only give an initial indication of the effects of whole-heart versus 2D perfusion CMR on estimates of ischemic burden, and direct comparisons between 2D and 3D imaging are needed in the future.

Although there was a difference in ischemic burden between the 3 slice and whole-heart analysis, there was no difference in assigning patients to either medical therapy when using a threshold of 10% ischemic burden. There was a trend toward a smaller ischemic burden from the 3-slice CMR analysis (6.8% versus 5.7%,  $P=0.03$ ). The lower ischemic burden is likely to be a consequence of the reduced number of slices influencing reporting of ischemia, leading to an underestimation of ischemia. Within its limitations, the comparison of whole heart versus 3-slice analysis raises questions about the relative benefits of spatial resolution, temporal resolution, signal-to-noise ratio, and cardiac phase that need to be explored in future studies. Further differences between the techniques are discussed in more detail elsewhere.<sup>26</sup>

## Limitations

This study investigated a population with a relatively high prevalence of scar, but we were primarily interested in the

**Table 3. MPS and CMR vs Coronary Angiography**

|       | Angiography: Significant Coronary Disease |         | Total |
|-------|---|---------|-------|
|       | Absent                                    | Present |       |
| CMR+  | 3   | 16      | 19    |
| CMR−  | 13  | 1       | 14    |
| Total | 16  | 17      | 33    |
| MPS+  | 6   | 16      | 22    |
| MPS−  | 10  | 1       | 11    |
| Total | 16  | 17      | 33    |

CMR indicates cardiovascular magnetic resonance; and MPS, myocardial perfusion scintigraphy.



**Table 4. Sensitivity and Specificity of MPS and CMR vs Coronary Angiography Stratified by Image Quality and Confidence Scores**

|                     | n  | Sensitivity | Specificity | Accuracy |
|---------------------|----|-------------|-------------|----------|
| <b>MPS</b>          |    |             |             |          |
| Confidence 3        | 10 | 100         | 80          | 90       |
| Confidence $\geq 2$ | 27 | 94          | 82          | 89       |
| Confidence $\geq 1$ | 33 | 94          | 63          | 79       |
| Quality 3           | 19 | 100         | 83          | 94       |
| Quality $\geq 2$    | 31 | 94          | 75          | 85       |
| Quality $\geq 1$    | 33 | 94          | 63          | 79       |
| <b>CMR</b>          |    |             |             |          |
| Confidence 3        | 18 | 100         | 100         | 100      |
| Confidence $\geq 2$ | 28 | 100         | 80          | 89       |
| Confidence $\geq 1$ | 33 | 94          | 81          | 88       |
| Quality 3           | 19 | 100         | 90          | 94       |
| Quality $\geq 2$    | 26 | 100         | 83          | 92       |
| Quality $\geq 1$    | 33 | 94          | 81          | 88       |

CMR indicates cardiovascular magnetic resonance; and MPS, myocardial perfusion scintigraphy.

assessment of ischemic burden independently of scar. The presence of scar may complicate the detection of superimposed inducible ischemia, and it is possible that the assessment of ischemia would be more accurate in populations without scar.

There were inevitable differences in the acquisition and measurement of ischemic volume between MPS and CMR. We equated the transmural of a CMR perfusion defect to the depth of the defect of tracer uptake on MPS. These 2 phenomena, although related, will not always be equivalent, potentially leading to differences in the estimation of ischemic burden. The method of establishing ischemic burden from the dynamic image series in first pass CMR is not identical to that used in MPS, which is based on multiple passes producing an average of distribution of tracer uptake.

The stress protocols differed slightly between MPS and CMR, leading to different hemodynamic parameters. Vasodilator stress using adenosine was used for both techniques because dynamic exercise was not possible during CMR. However, when adenosine is used for MPS, it is desirable to combine it with submaximal dynamic exercise to reduce side effects and extracardiac uptake of tracer. The accuracy of adenosine MPS with and without additional exercise is similar, and the difference between stress techniques would not be expected to have affected the findings.<sup>27</sup>

Our results can only give an indication of the relative performance for conventional 3-slice 2D CMR perfusion imaging. Only an adequately powered head-to-head comparison of the 2 acquisition (2D versus 3D) methods can give conclusive evidence of their accuracy in determination of ischemic burden. However, as demonstrated in this study and observed in phantoms studies,<sup>5</sup> 3D whole-heart acquisition seems to provide a more accurate estimation of ischemic burden than using 3-slice acquisition.

Our analysis method used the clinical standard of visual measurement of ischemic burden. Quantitative analysis methods have important potential advantages such as higher

objectivity and the detection of balanced ischemia but have not yet been applied to 3D CMR perfusion data sets.

## Conclusions

Estimates of ischemic burden from 3D myocardial perfusion CMR agreed closely with MPS. The technique was also accurate for the detection of angiographically defined coronary obstruction. Combined with CMR assessment of cardiac function and viability, 3D myocardial perfusion CMR holds promise as a complete noninvasive and radiation-free diagnostic and risk stratification tool for patients with known or suspected CAD.

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## Disclosures

None.

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### CLINICAL PERSPECTIVE

Myocardial perfusion cardiovascular magnetic resonance (CMR) has become an established method for the noninvasive diagnosis of coronary artery disease (CAD). Although this technique may be useful for diagnostic purposes, the selective spatial coverage may prevent an accurate measurement of ischemic burden. In clinical practice, ischemic burden is most commonly measured by myocardial perfusion scintigraphy (MPS). It is an important prognostic factor in CAD and in accordance with guidelines can help identify patients who will benefit most from revascularization compared with medical therapy. Three-dimensional (3D) myocardial perfusion CMR techniques overcome the problem of limited cardiac coverage and are also accurate in the detection of CAD. Measurements of ischemic burden from 3D myocardial perfusion CMR have been shown to agree with invasive indices of myocardium at risk and to reduce following percutaneous coronary intervention. However, a direct comparison with MPS has not previously been reported. This study compared ischemic burden between MPS and 3D myocardial perfusion CMR in 45 patients. The mean ischemic burden was similar, and there was a strong correlation between techniques. In a subset of these patients, the diagnostic accuracy of the 2 methods against invasive coronary angiography was also assessed and noted to be similar. 3D myocardial perfusion CMR may be considered an alternative to MPS for detecting the presence and rating the severity of ischemia with the added benefits of higher spatial resolution and no exposure to ionizing radiation. In accordance with current guidelines the recently proposed 3D myocardial perfusion CMR may help identify patients who will benefit most from revascularization compared with medical therapy. Our data suggest that a similar threshold of 10% ischemic burden as used to guide the management of patients with CAD with MPS can also be applied to 3D myocardial perfusion CMR. However, larger studies powered to determine the use of 3D myocardial perfusion CMR as a noninvasive strategy for the diagnosis and risk stratification of patients with suspected CAD are required to fully address this question.